

Remarks

I. Status of the Application and Claims

As originally filed, the present application had a total of 17 claims. Claims 1-4, 8, and 10-17 were withdrawn as the result of a restriction requirement. The remaining claims were eventually cancelled and were replaced with claims 18-40. Claims 27-29 have been cancelled herein. Thus, the claims now pending are 18-26 and 30-40.

II. Request for Cancellation of Withdrawn Claims

Applicants hereby formally request that claims 1-4, 8 and 10-17, which were withdrawn as the result of a restriction requirement, now be cancelled.

III. The Amendments

Applicants have cancelled claims 27-29 herein. This was done in order to advance the prosecution of the present application and cancellation should not be taken as an indication that Applicants are in agreement with any of the Examiner's rejections. These claims may, optionally, be pursued by Applicants in a future continuation application.

Claim 39 was amended to reflect the cancellation of claims 27-29. This amendment clearly does not add new matter to the application and its entry is therefore respectfully requested.

IV. Submission of Information Disclosure Statement

On page 3 of the Office Action, the Examiner indicates that an Information Disclosure Statement filed by Applicants is missing from the file and requests that we resubmit it along with the cited references. In compliance, Applicants are resubmitting the Information Disclosure Statement that was originally filed on June 17, 2002, along with copies of the cited references.

V. Claim Objections

On page 3 of the Office Action, the Examiner objects to claims 27-29, 39 and 40 because claim 27 includes a peptide sequence that has not been given a sequence identification number. Since claim 27 has now been cancelled and claim 39 has been amended so that it is no longer

dependent upon claim 27, Applicants respectfully submit that the Examiner's objection has been obviated.

The Rejections

I. Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

On pages 2 and 3 of the Office Action, the Examiner rejects claims 27-29 under 35 U.S.C. § 112, second paragraph. However, since Applicants have cancelled these claims herein, it is respectfully submitted that the Examiner's rejection has been obviated.

II. Second Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

On pages 3 and 4 of the Office Action, the Examiner makes a second rejection of claims 27-29, 39 and 40 under 35 U.S.C. § 112, second paragraph. It is alleged that claim 27 recites "polynucleotide is at least ten amino acids in length" and that this phrase is unclear. Although Applicants do not agree that claim 27 is indefinite, it has now been cancelled and the Examiner's rejection has therefore been obviated.

III. Rejection of Claims Under 35 U.S.C. § 101

On pages 4-7 of the Office Action, all pending claims are rejected based upon the utility requirement of patentability. The Examiner alleges that, although Applicants have identified a novel gene and shown that the proteins it encodes are homologous to two multidrug resistance proteins, homology studies alone are insufficient to establish function. Several scientific articles are cited in support of this argument. The Examiner also argues that Applicants did not use proper controls in their studies and that it is unclear whether the overexpression of proteins reported by Applicants occurs *in vivo* or simply in cultured cells. Based upon these considerations, the Examiner concludes that Applicants' asserted utility is not credible.

Applicants respectfully traverse this rejection.

The Examiner is correct in his assertion that patent law requires that an application assert a utility for a claimed invention which is substantial, specific and credible. In the case of the present application, Applicants have identified a new gene which, through differential splicing,

may produce eight different polypeptides (designated as SEQ ID NO:1-SEQ ID NO:8). Based upon the studies more fully discussed below, Applicants have concluded that newly discovered gene is involved in multidrug resistance and, as a result, have proposed several different utilities. In particular, they have asserted: (a) that overexpression of the gene may be used as a marker for identifying cells likely to display multidrug resistance and which are therefore likely to respond to therapies aimed at reducing such resistance (see page 8 of the application, line 39 - page 9, line 2); (b) that certain polypeptide splice variants (SEQ ID NO:1-6) which are selectively expressed in cancer cells but not in non-cancer cells should make good diagnostic markers and good targets for therapeutic agents (*e.g.*, a monoclonal antibody coupled to a cytotoxic agent, see page 5, lines 13-33); and (c) that assays for other polypeptide splice variants (SEQ ID NO:7 and SEQ ID NO:8) may be used to identify pluripotent stem cells and to enrich cell populations in these cells (see page 6, lines 1-10).¹ Apart from this, Applicants have asserted that the newly discovered gene may be used in assays designed to identify agents that inhibit its biological activity and which would therefore have potential value as adjuncts in cancer chemotherapy.

The Examiner has argued that Applicants' utility is not specific because cells in culture may not behave the same as cells *in vivo*. However, some of the utilities asserted in the application do not depend at all on whether the cells have undergone changes *in vitro* or not. For example, the identification of agents that inhibit multidrug resistance would remain as an important use for the gene even if the assays used were only carried out in cultured cells. Apart from this, Applicants do not see any basis for concluding that culturing cells would increase the expression of a multidrug resistance gene. The types of changes which would appear to be most likely to occur in cell culture would be those which better adapt cells for growth in a culture environment. In the absence of this, or some other, basis for believing that cell culture would lead to the overexpression of genes involved in multidrug resistance, the suggestion that the overexpression reported by Applicants is merely an artifact is not warranted.

¹ The utility of genes and the proteins that they encode are clearly interrelated. For example, the DNA can be used to make the protein which, in turn, can be used to make antibodies for quantitating gene expression or for inhibiting the action of the protein.

In light of the above considerations, Applicants submit that at least one utility that has been asserted in the application is specific (not all proteins can be used in assays for identifying potential therapeutic agents) and substantial (the identification of potential new therapeutic agents based upon *in vitro* assays has been recognized by the Patent Office in its utility guidelines as being sufficient to support patentability). As discussed in MPEP § 2107, *et seq.*, once a utility of this type has been set forth in an application, the only remaining basis for rejecting claims is that this utility is not credible.

In order to be credible, it is not necessary for an applicant to show that an invention works with absolute certainty and the requirements of patentability can be met even though considerable further research and development are needed before an invention could actually be used (see quotation of *In re Brana*, 51 F.3d 1560 (1995) in MPEP). The relevant test for credibility is set forth in the Manual as follows:

An assertion is credible unless (a) the logic underlying the assertion is seriously flawed or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion.

In the present case, Applicants have set forth a number of facts upon which they have concluded that the newly identified gene is involved in multidrug resistance. As recognized by the Examiner, one factor relied upon is structural homology studies. Although sequence homology data may not be conclusive as to function, there is no question that it is accepted in the art that the greater the degree of structural homology exhibited by proteins, the stronger is the probability that they will exhibit similar functions.² In the present case, Applicants report a 68% sequence homology between the proteins that they have identified and two proteins known to be involved in multidrug resistance (MDR1 and MDR2). This is clearly a very high degree of homology and strongly suggests that all of these proteins probably serve in transporting drug across cell membranes.

² The references cited by the Examiner point to limitations on the use of sequence homology data but none of these references suggest that such data is not a good predictive tool.

In addition, the application reports that the newly identified gene is preferentially expressed in tissues where multidrug resistance would be expected. Specifically, using PCR analysis, immunostaining and flow cytometry, it was found that all of the proteins are highly expressed in cancer cells with preferential expression occurring in melanoma cells for six of the eight splice variant proteins (see page 18, lines 14-22 and 29-32, and page 19, lines 4-9).

Finally, the application discloses functional studies which directly show that the new gene acts as a transporter and protects cells from chemotherapeutic agents (see page 18 of the application, line 24 - page 19, line 15). These results are not mentioned in the Office Action and may not have been taken into account by the Examiner. Experiments were performed to determine the effect of antibodies against the splice variant proteins on dye transport across cell membranes and on the susceptibility of cells to being killed by cisplatin, a commonly used chemotherapeutic agent. It was found that the antibodies both inhibited dye transport and enhanced the cytotoxicity of the cisplatin. Thus, Applicants have provided direct experimental evidence that the proteins act as transporters and help to make cells resistant to cytotoxic drugs.

In summary, Applicants have direct experimental evidence that: (1) there is a high (68%) degree of structural homology between their proteins and those known to be involved in multidrug resistance; (2) there is a high degree of expression of the newly identified gene in cells where multidrug resistance would be expected; (3) the proteins identified act as transporters as determined using antibody studies; and (4) the proteins reduce the cytotoxicity of cells to at least one chemotherapeutic drug (cisplatin) as also determined using antibody studies.

Applicants submit that, when the above factors are considered as a whole, the suggestion that the gene discovered by Applicants acts in multidrug resistance is credible. There is no basis for concluding that the logic leading to Applicants' asserted utility is flawed or that the facts upon which the assertion is based are inconsistent with this logic.

In light of the above considerations, Applicants respectfully submit that the present application sets forth at least one utility which meets all of the requirements of patentability. It is therefore respectfully requested that the Examiner's rejection be withdrawn.

IV. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

On page 7 of the Office Action, the Examiner rejects claims 18-40 under 35 U.S.C. § 112, first paragraph. It is asserted that the claimed invention is not supported by a specific, substantial and credible utility. As a result one skilled in the art would not know how to use the invention.

For the reasons set forth above, Applicants believe that the claimed invention is, in fact, supported by an appropriate utility. It is therefore respectfully submitted that the Examiner's rejection under 35 U.S.C. § 112, first paragraph, has been overcome.

Conclusion

In light of the amendments and discussion above, Applicants submit that all of the Examiner's rejections have been overcome. It is therefore respectfully requested that these rejections be withdrawn and that the claims presently pending in the application be allowed.

If, in the opinion of the Examiner, a phone call may help to expedite the prosecution of this application, the Examiner is invited to call Applicants' undersigned attorney at (202) 419-7013.

Respectfully submitted,

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Appendix

Version with Markings to Show Changes Made

Claim 39 was amended herein. The claim is rewritten below with the bracketed portions indicating text that was removed and the underlined portions indicating text that was added.

39. (Amended) A vector comprising a distinct coding element consisting of the nucleotide sequence of the polynucleotide of any one of claims [19-29]19-26 or 31-38.